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~~42~~. A low salt-containing composition comprising biologically active recombinant human IGF-I in a concentration of about 350 mg/ml, wherein said composition has a density of about 1.07 g/ml and a viscosity of about 15,700 cps.

B7 cancel

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~~43~~. A pharmaceutical composition comprising the composition of claim ~~42~~.

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~~44~~ 24 A cryogenically produced PLGA microsphere comprising the composition of claim ~~42~~.--

REMARKS

Claims 1, 3, 4, 13, 16, 19, and 20 have been amended for purposes of clarification. Support for the amendments to the claims resides throughout the specification, particularly at pages 2, 4, 8, 9, 12-18, and 20, and in the original claims. Claims 2, 8, and 12 have been canceled without prejudice or disclaimer. New claims 28-42 have been added. Support for the new claims resides throughout the specification and in the original claims. No new matter is added by way of claim amendment. Claims 1, 3, 4, 13, 16-20, and new claims 28-42 are pending prosecution in this Official Action. The Examiner's remarks in the Official Action are addressed below in the order set forth therein.

Consideration of Previously Submitted Information Disclosure Statement

It is noted that an initialed copy of the complete PTO Form 1449 that was submitted with Applicants' Information Disclosure Statement filed March 19, 1999, and an initialed copy of the PTO Form 1449 that was submitted with Applicants' Supplemental Information Disclosure Statement filed May 19, 1999 have not been returned to Applicants' representative with the Office Action. Accordingly, it is requested that an initialed copy of each Form 1449 be forwarded to the undersigned with the next communication from the PTO. In order to facilitate review of the references by the Examiner, a copy of the Information Disclosure Statement and the Supplemental Information Disclosure Statement with their respective Form 1449 are attached

hereto. Copies of the cited references were provided at the time of filing the original Information Disclosure Statements, and, therefore, no additional copies of the references are submitted herewith. Applicants will be pleased to provide additional copies of the references upon the Examiner's request if it proves difficult to locate the original references.

The Invention

The present invention is directed to low salt-containing compositions that comprise biologically active human IGF-I or biologically active variant thereof in a concentration of at least about 250 mg/ml, where the variant is a polypeptide that has IGF-I activity and differs from the amino acid sequence for human IGF-I by up to 10 amino acid residues. The compositions comprise a highly concentrated, precipitated form of human IGF-I or variant thereof that has the consistency of a viscous syrup. The precipitation process is completely reversible. Thus, the IGF-I or variant thereof in the form of this viscous syrup can be resolubilized, and the resulting soluble form of the polypeptide retains its full biological activity without the need for refolding.

The compositions find use in preparing biologically active human IGF-I or biologically active variant thereof in a highly concentrated form that is useful, for example, as a means of storing the IGF-I or variant thereof and for making pharmaceutical compositions. This highly concentrated form of human IGF-I or variant thereof has the additional benefit of being prepared in the absence of metal complexing or salt precipitation, two processes used for obtaining concentrated protein compositions. Unlike metal-complexed or salt-precipitated concentrated preparations of proteins, the concentrated protein of the present invention can be used directly in pharmaceutical compositions without the concern for pharmaceutically undesirable concentrations of metals or salts in the end product.

The Objection to the Specification Is Overcome

The specification is objected to because of blank spaces on pages 2, 8, and 14, lines 2, 6, and 29, respectively. At these places in the specification Applicants make reference to an application that was filed concurrently with the present application. Thus, at the time of filing,

the U.S. Serial Number for the concurrently filed application was not available. Applicants have amended the specification to include the Serial Number corresponding to the concurrently filed application. No new matter is added by way of this amendment.

The Rejections of the Claims Under 35 U.S.C. §112, First Paragraph, Should Be Withdrawn.

Claims 1-4, 8, 12, 13, and 16-20 are rejected under 35 U.S.C. §112, first paragraph. Claims 2, 8, and 12 have been canceled without prejudice or disclaimer. This rejection is respectfully traversed as it applies to the remaining amended claims.

Claims 1, 3, 4, 13, and 16-20 as amended are directed to compositions comprising biologically active human IGF-I or biologically active variant thereof, where the variant is a polypeptide that has IGF-I activity and differs from the amino acid sequence for human IGF-I by up to 10 amino acid residues. Support for amendments to the claims resides in the specification. See, for example, page 2, line 18, page 4, lines 11-13, and original claim 2, where the composition is defined as being "low salt-containing"; page 8, line 23, where biologically active variants are described; page 8, lines 24-25 and lines 25-31, where variants having IGF-I activity and assays for determining IGF-I activity are described; page 9, lines 19-21, where it is noted that variants can differ by up to 10, 5, 4, 3, 2, or 1 amino acid residues; page 11, lines 23-24, where it is stated that the human IGF-I gene is known; page 11, lines 29-30, and page 20, lines 13-15, where production of recombinant human IGF-I in International Application Nos. WO 96/07424 and WO 96/40776 and U.S. Patent Nos. 5,324,639, 5,324,660, and 5,650,496 is described. No new matter is added by way of claim amendment.

Original claims 1-4, 8, 12, 13, and 16-20 are rejected as containing subject matter not described in the specification in such a way as to enable one of skill in the art to make and/or use the invention. The Official Action asserts that the use for variants of IGF-I has not been shown, and that modification of the native sequence to obtain the variant polypeptide could result in loss of secondary and tertiary structure, and thus biological activity. Applicants respectfully traverse this rejection.

The specification provides a written description of what the term "biologically active variants" of IGF-I encompasses. See particularly, pages 9-10. Further, the specification indicates that biologically active variants of IGF-I have an IGF-I activity and an amino acid sequence that differs from the reference IGF-I sequence, in this case human IGF-I, by up to 10 amino acid residues. The amino acid sequence of human IGF-I is known in the art. The specification cites International Patent Application Nos. WO 96/07424 (at page 11, lines 28-30) and WO 96/40776 and U.S. Patent Nos. 5,324,639, 5,324,660, and 5,650,496 (at page 20, lines 13-15) as disclosing recombinant production of human IGF-I, the sequence of which is set forth therein. The present specification describes in detail how modifications of the reference sequence, i.e., human IGF-I, can be made to obtain biologically active variants of human IGF-I. See for example pages 9-11. Specific examples of IGF-I variants known in the art are given in the specification at page 10, lines 24-31, through page 11, line 2. Further, the variant of human IGF-I that serves as the starting material for making the claimed compositions exhibits IGF-I biological activity. See, for example, the specification at page 8, lines 24-26. The variant polypeptide, when prepared in its syrup form, retains its full biological activity when reconstituted from this syrup form into a solution, without the need for refolding. See, for example, the specification at page 4, lines 13-15, and page 6, lines 23-29. Thus, the variant IGF-I molecule present in the claimed compositions retains a secondary and tertiary structure that supports IGF-I biological activity when reconstituted into solution.

Under the first paragraph of 35 U.S.C. §112, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it. See *In re Frimme, Deil, and Schmitz*, 124 U.S.P.Q. 499, 502 (C.C.P.A. 1976). The mere breadth of the claims is not a basis for determining sufficiency of a specification. See *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971). In an unpredictable art, the Applicant is not required to test every species covered by a claim and include them in the application. See *In re Anderson*, 176 U.S.P.Q. 331, 333 (C.C.P.A. 1973). Otherwise, the inventor seeking adequate patent protection would be forced to carry out a prohibitive number of actual experiments, and this would necessitate the application to include "thousands" of examples. See *id.* The mere possibility of inclusion of

inoperative substances does not prevent allowance of broad claims. See *In re Kamal and Rogier*, 158 U.S.P.Q. 320, 324 (C.C.P.A. 1968).

Applicants respectfully submit that given the disclosure of the present invention, particularly the methods described on pages 5-8 and Examples 2 and 3, one of skill in the art could take a polypeptide that represents a biologically active variant of IGF-I, where the variant has IGF-I activity and differs from the amino acid sequence of human IGF-I by up to 10 amino acid residues, and readily use it in accordance with the novel methods of the present invention to obtain the claimed compositions. Thus, the requirement under 35 U.S.C. §112, first paragraph, that the disclosure be sufficient to teach one of skill in the art what the invention is and how to practice it has been met. Therefore, this rejection as applied to the amended claims should be withdrawn.

Claims 16-20 are rejected for lack of description of the claimed subject matter. This rejection is respectfully traversed as applied to the amended claims.

Pharmaceutical compositions comprising the novel low salt-containing compositions of the invention are described in the specification at pages 13-18. Cryogenically produced PLGA microspheres containing the novel low salt-containing compositions of the invention are described in the specification at page 20, lines 3-8, and Examples 6 and 7, page 24. Applicant respectfully submits that the disclosure is sufficient to teach one of skill in the art what these claimed compositions are and how to make and use them. Accordingly, this rejection of the claims should be withdrawn.

Claims 1, 4, 8, 13, and 16-20 are rejected under 35 U.S.C. §112, first paragraph, as based on a disclosure that is not enabling. Claim 8 has been canceled. This rejection is respectfully traversed as it applies to the remaining amended claims.

The Official Action states that the phrase "low salt-concentration" is critical or essential to the practice of the invention, that this phrase is not included in the claims, and that this phrase is not enabled by the disclosure. Applicants respectfully submit that this phrase is included in

independent claim 1 as amended, and hence in dependent claims 3, 4, 13, and 16-20, all of which now depend directly or indirectly from independent claim 1. Applicants submit that this phrase is enabled by the disclosure.

In the present invention, the phrase "low salt-containing" is defined as an amount of salt that is insufficient to cause precipitation of the protein. See the specification at page 4, lines 11-13. One of skill in the art would recognize this as an amount of salt that is less than the amount of salt needed to cause precipitation, or so-called "salting out" of a protein. The specification provides guidance as to the determination of the "salting-out" point of a protein, i.e., the amount of salt needed to cause precipitation of a protein. As further guidance, Applicants provide an illustration of a salt-precipitated IGF-I composition in Example 5 at page 23 of the specification, and contrast the characteristics of this composition with the novel low salt-containing IGF-I composition of the invention. See pages 4, lines 17-19, and Example 5, page 23. Given Applicants' disclosure, one of skill in the art could readily determine the amount of salt necessary to achieve the "salting-out" point of IGF-I, and, having determined this, could readily determine how much salt could be present in the novel IGF-I compositions of the invention before salt-precipitation of the IGF-I would occur.

In view of these remarks, Applicants respectfully submit that the phrase "low salt-containing" is enabled and that claims drawn to low salt-containing compositions comprising biologically active human IGF-I or variant thereof are also enabled by the specification. Accordingly, the rejection of the claims under 35 U.S.C. §112, first paragraph, should be withdrawn.

The Rejections of the Claims Under 35 U.S.C. §112, Second Paragraph, Should Be Withdrawn

Claims 1-4, 8, 12, 13, and 16-20 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Claims 2, 8, and 12 have been canceled as noted above. This rejection is respectfully traversed as applied to the remaining amended claims.

These claims are rejected for recitation of the term "variant thereof" as it renders the claims indefinite as to the claims' meets and bounds. The remaining claims have been amended

to clarify that the composition comprises human IGF-I or variant thereof, where the variant is a polypeptide that has IGF-I activity and differs from the amino acid sequence of human IGF-I by up to 10 amino acid residues. Support for these amendments to the claims resides in the specification, as noted above. No new matter is added by way of claim amendment.

Applicants respectfully submit that these claims as amended are definite and distinctly claim the subject matter that Applicants regard as the invention. Therefore, this rejection of the claims under 35 U.S.C. §112, second paragraph, should be withdrawn.

Claims 1-4, 8, 12, 13, and 16-20 are also rejected under 35 U.S.C. §112, second paragraph, for recitation of the phrases "highly concentrated" and "low-salt", as use of these terms renders the claims indefinite as to the claims' meets and bounds. This rejection is respectfully traversed.

The phrase "highly concentrated" and the term "low-salt" are both defined in the specification. See particularly, page 4, lines 1-4, where "highly concentrated" is defined as an IGF-I concentration of at least about 250 mg/ml as measured at ambient temperature. See page 4, lines 11-13, where "low-salt containing" is defined as an amount of salt that is insufficient to cause precipitation of the protein. Applicants respectfully submit that one of skill in the art would understand the meets and bounds of the terminology in these claims in view of the specification, particularly the Examples described therein. Further, the specification provides guidance as to the determination of the "salting-out" point of a protein, i.e., the amount of salt needed to cause precipitation of a protein. See page 4, lines 17-29, and Example 5, page 23, where the distinction between the novel IGF-I composition of the invention and a salt-precipitated IGF-I composition is described. At page 4, lines 22-23, of the specification Applicants also reference pages 79-81 of Voet and Voet's standard biochemistry textbook for additional guidance as to the distinction between the IGF-I composition of the invention versus a salt-precipitated IGF-I composition. Thus, Applicants respectfully submit that the phrases "highly concentrated" and "low salt-containing" are definite.

For purposes of expediting prosecution, claims 1, 3, 4, 13, and 16-20 as amended do not use the phrase "highly concentrated". The phrase "highly concentrated" is not considered necessary, as the claims clearly set forth that the low salt-containing composition comprises human IGF-I or variant thereof in a concentration of "at least about 250 mg/ml".

In view of these remarks, Applicants respectfully submit claims 1, 3, 4, 13, and 16-20 are definite and distinctly claim the subject matter Applicants regard as their invention. Accordingly, this rejection of the claims under 35 U.S.C. §112, second paragraph, should be withdrawn.

Claims 1, 8, and 12 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite and duplicative of one another, as they are drawn to substantially the same composition of matter. This rejection is respectfully traversed.

Claim 1 as amended definitively describes the novel low salt-containing composition comprising biologically active human IGF-I or variant thereof, as noted above. Claims 8 and 12 have been canceled without prejudice or disclaimer. Thus this rejection is obviated by way of amendment to the claims.

Claims 16-20 are rejected under 35 U.S.C. §112, second paragraph, for recitation of the term "container means". This rejection is respectfully traversed.

Applicants respectfully submit that claims 16-20 do not recite this term. Applicants have, however, amended claim 13 to omit reference to a "means" clause and a compartmentalized "carrier" so as to clarify that part of the invention encompassed by this claim. The kit of claim 13 comprises the novel low salt-containing composition comprising biologically active human IGF-I or biologically active variant thereof recited in claim 1, and a buffered solution for reconstituting a pharmaceutical composition comprising biologically active human IGF-I or biologically active variant thereof. No new matter is added by way of this amendment. In view of these remarks, Applicants respectfully submit that this rejection should be withdrawn.

Claims 2-4 are rejected under 35 U.S.C. §112, second paragraph, for recitation of the phrase "a low salt-containing" without antecedent basis in claim 1, from which they depend. This rejection is respectfully traversed.

Applicants respectfully submit that the rejection with regard to claim 2 is obviated by cancellation of this claim. Further, claims 3 and 4 as amended depend from claim 1, which does recite this phrase. Thus, this rejection of these claims should be withdrawn.

Claims 1-4, 8, 12, and 13 are rejected under 35 U.S.C. §112, second paragraph, as being improper composition claims as they are drawn to a compound. Claims 2, 8, and 12 have been canceled as noted above. This rejection is respectfully traversed as applied to the remaining amended claims.

Claims 1, 3, 4, and 13 are drawn to a low salt-containing composition that comprises biologically active human IGF-I or biologically active variant thereof in a concentration of at least about 250 mg/ml. This composition has, as an additional property, the consistency of a viscous syrup. It is a composition of matter not found in nature. The starting material for this composition can be purified native, recombinantly produced, or chemically synthesized human IGF-I or variant thereof as defined in these claims. The resulting composition is not a "compound" as defined by one of skill in the art, but rather a highly concentrated, precipitated form of human IGF-I protein or variant thereof whose basic subunit resides in its individual amino acid residues. As such, Applicants respectfully submit that claims 1, 3, 4, and 13 are drawn to compositions, and the rejection of these claims under 35 U.S.C. §112, second paragraph, should be withdrawn.

The Objection to the Claims Is Overcome

Claims 16-20 are objected to because they depend from a non-elected claim, claim 15. This objection is traversed as it applies to the amended claims.

Independent claims 16 and 19 as amended are directed to compositions that comprise the novel low salt-containing composition comprising biologically active human IGF-I or

biologically active variant thereof as described in the specification and recited in claim 1. Support for these amendments to the claims resides in the specification, for example at pages 12-18, where various pharmaceutical compositions comprising this novel IGF-I composition are described, and at pages 20, lines 3-8, and page 24, Examples 6 and 7, where encapsulation of the novel low salt-containing composition comprising IGF-I into microspheres is described.

In view of these remarks, Applicants respectfully submit that the objection to these claims is overcome and should be withdrawn.

The Rejection of the Claims Under 35 U.S.C. §103(a) Should Be Withdrawn

Claims 1-4, 8, 12, 13, and 16-20 are rejected under 35 U.S.C. §103 (a) as being unpatentable over Johnson *et al.* (1996) *Nature Medicine* 2(7):795-599. This rejection is respectfully traversed as it applies to the amended claims.

Claims are not obvious under 35 U.S.C. §103 (a) if they are not suggested in the combined teachings of the references to a person having ordinary skill in the art. See *In re Keller*, 208 U.S.P.Q. 871, 881(C.C.P.A. 1981). To establish a prima facie case of obviousness, the Patent Office must set forth the differences in the claimed invention over the applied references and the proposed modification of the references that would be necessary to arrive at the claimed subject matter, and explain why the proposed modification would be obvious. See *Graham v. John Deere Co.*, U.S.P.Q. 459, 467 (U.S., 1966). Under this rule, claims are not obvious if they are sufficiently different from and not suggested by the prior art. The inquiry surrounding the establishment of a prima facie case of obviousness needs not concern whether the claimed invention is better than the prior art.

Johnson *et al.* teach microencapsulation of a lyophilized zinc-complexed rhGH to obtain an injectable sustained-release form of this protein. The lyophilized zinc-rhGH protein complex is encapsulated within a PLGA microsphere along with additional zinc carbonate salt. The concentration of hGH stored within the PLGA microspheres is comparable to that in the somatotrophic granules of the pituitary, that is 50-100 mg/ml (at page 797, column 2, Discussion, lines 4-6). The reference teaches that complexing the protein with zinc prior to lyophilization

and encapsulation enhances the stability of the protein, as the protein is present within the hydrated microsphere as an insoluble zinc complex that maintains its native properties and structure. Further, Johnson *et al.* suggest that "the particles of zinc salt [within the microspheres] provide additional zinc to maintain the protein in the complexed form or that the protein binds to the solid zinc salt" (at page 798, column 1, lines 7-9). By complexing the rhGH with zinc and including the zinc carbonate salt in the microspheres, the encapsulated protein is also released in a slower fashion (at page 798, column 1, lines 4-6). If the zinc and zinc carbonate salt are not included in the microspheres, the protein forms aggregates (at page 796, column 1, lines 11-21) and is released at a faster rate (at page 798, lines 4-6). Thus, the Johnson *et al.* reference teaches that complexing rhGH protein with zinc to obtain an insoluble rhGH protein for packaging within a microsphere with additional zinc carbonate salt is advantageous to protein stability and protein release from a sustained-release formulation. Further, Johnson *et al.* teach that encapsulation of rhGH in the PLGA microspheres allows for lowering the overall dose of rhGH that is delivered to a patient over time (at page 798, column 1, lines 42-49). However, Johnson *et al.* do not teach or suggest the present invention as claimed.

The present invention is directed to a novel low salt-containing composition that comprises biologically active human IGF-I or biologically active variant thereof in a concentration of at least about 250 mg/ml (claim 1). The kit, pharmaceutical composition, and cryogenically produced PLGA microspheres of the present invention comprise this novel composition. Johnson *et al.* do not teach or suggest such a composition. As the IGF-I composition of claim 1 is novel and non-obvious, compositions comprising it are novel as well.

Further, zinc, which serves as a critical component for stabilization of rhGH in the PLGA microspheres taught by Johnson *et al.*, does not readily bind to human IGF-I. See Slieker (1994) "Insulin and IGF-I Analogues: Novel Approaches to Improved Insulin Pharmacokinetics," in *Current Directions in Insulin-like Growth Factor Research*, ed. Leroith and Raizada (Plenum Press, NY), pp. 25-32, a copy of which is submitted concurrently herewith. Thus, it would not be advantageous to complex the IGF-I composition of the invention with zinc prior to

encapsulating this novel IGF-I protein composition within a PLGA microsphere using the cryogenic process disclosed in Johnson *et al.*

As the Johnson *et al.* reference neither teaches nor suggests either the novel low salt-containing IGF-I composition of the invention, nor kits, pharmaceutical compositions, or PLGA encapsulated microspheres comprising this composition, Applicants respectfully submit that a prima facie case of obviousness has not been established. Therefore, the rejection of the claims under 35 U.S.C. §103(a) should be withdrawn.

New Claims

Claims 28-44 have been added. The new claims set forth narrow embodiments of claim 1. Specifically, claims 28-30 further define the amino acid sequence of the variant IGF-I polypeptide as differing from the human IGF-I sequence by up to 5, up to 2, or 1 amino acid residue. Claims 31-33 further define the composition of claim 1, where the human IGF-I is recombinant human IGF-I. Independent claim 34 and its dependent claims 35-41 are narrowly drawn to a low salt-containing composition comprising biologically active human IGF-I, while independent claim 42 and its dependent claims 43 and 44 are narrowly drawn to a low salt-containing composition comprising biologically active recombinant human IGF-I in a given concentration, where the composition has a particular density and viscosity. Support for these new claims resides in the specification. See, for example, page 9, lines 19-21, where variants differing by up to 5, 2, or 1 amino acid residue are disclosed; page 11, lines 23-24, where it is stated that the human IGF-I gene is known; page 11, lines 28-30, and page 20, lines 13-15, where production of recombinant human IGF-I is described. Dependent claims 32, 33, 36, and 37, and independent claim 42 recite further limitations as to the concentration of human IGF-I or recombinant human IGF-I, while dependent claims 33 and 37, and independent claim 42 recite the density and viscosity of the low salt-containing composition. Support for these new claims resides throughout the specification as noted above and in the original claims.

No new matter is added by the inclusion of these new claims. As these claims reflect the amendments noted for pending claims 1, 3, 4, 13, and 16-20, Applicants respectfully submit that these claims are definite, fully enabled by the specification, novel, and non-obvious.

Applicants' Response to Restriction Requirement

The Official Action indicates that Applicants elected with traverse, then failed to present any reason(s) for the traversal of the requirement. Applicant respectfully note that in the Response to Restriction Requirement dated June 18, 1999, election of Group I invention was made without traverse.

CONCLUSION

In view of the above amendments and remarks, Applicants submit that the rejections of the claims under 35 U.S.C. §112, first and second paragraph, and under 35 U.S.C. §103(a) are overcome. Applicants respectfully submit that this application is now in condition for allowance. Early notice to this effect is solicited.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject Application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner For Patents, Washington, DC 20231, on November 15, 2000.

Polly P. Burton

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